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WO 00/71124 A1

(54) Title: AMORPHOUS FORM OF FEXOFENADINE HYDROCHLORIDE

(57) Abstract: This invention relates to an amorphous form of fexofenadine hydrochloride, to a process for the preparation thereof, and to a composition containing it.

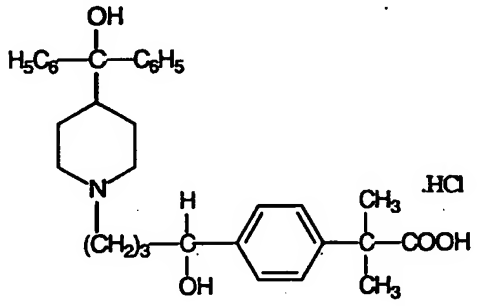
AMORPHOUS FORM OF FEXOFENADINE HYDROCHLORIDE

FIELD OF THE INVENTION

This invention relates to an amorphous form of fexofenadine hydrochloride, to a process for the preparation thereof, and to a composition containing it.

BACKGROUND OF THE INVENTION

Chemically, fexofenadine is 4-[4-[4-hdroxydiphenylmethyl)-1-piperidinyl]-hydroxybutyl]-α, α-dimethylbenzene acetic acid also known as terfenadine carboxylic acid metabolite having the Formula I.



Formula I

Fexofenadine hydrochloride (Terfenadine carboxylic acid hydrochloride) is an effective antihistamine which avoids adverse effects associated with the administration of terfenadine including abnormal heart rhythms in some

patients with liver disease or who also take the antifungal drug ketoconazole or the antibiotic erythromycin.

The pharmaceutical industry has, of late, conducted studies on polymorphism in drugs and the difference in the activity of different polymorphic forms of a given drug. By the term polymorphism we mean to include different physical forms, crystal forms, crystalline/liquid crystalline/non-crystalline (amorphous) forms. This has especially become very interesting after observing that many antibiotics, antibacterials tranquilizers etc, exhibit polymorphism and some/one of the polymorphic forms of a given drug exhibit superior bio-availability and consequently show much higher activity compared to other polymorphs. It has also been disclosed that the amorphous forms in a number of drugs exhibit different dissolution characteristics and in some cases different bioavailability patterns compared to the crystalline form [Konne T., Chem. Pharm. Bull. 38, 2003 (1990)]. For some therapeutic indications one bioavailability pattern may be favoured over another. Cefuroxime axetil is a good example of an amorphous form exhibiting higher bioavailability than the crystalline form. Sertraline, Frentizole, Sulphathiazole, Indomethacine, etc., are some of the important examples of pharmaceuticals which exhibit polymorphism. A number of patents have been granted pertaining to these new forms of old drugs. To cite a few, US Patent No. 5,248,699 discloses five polymorphic forms of sertraline hydrochloride while EP 014490 describes four polymorphic forms of Frentizole. EP 490648 and EP 022527 also deal with the subject of polymorphism in drugs.

PCT patent application WO 95/31437 discloses fexofenadine hydrochloride in various new crystalline forms designated Form I, Form II and Form IV and methods for their preparation.

SUMMARY OF THE INVENTION

The first object of the present invention is to provide fexofenadine hydrochloride in an amorphous form. The amorphous form of fexofenadine hydrochloride is prepared by an efficient process which uses conditions which are convenient to operate on a commercial scale and operationally safe.

The second object of the present invention is to provide a process for the preparation of fexofenadine hydrochloride in an amorphous form which comprises dissolving crystalline fexofenadine hydrochloride in a suitable solvent or dissolving fexofenadine base in a suitable solvent and adding a suitable solvent containing hydrogen chloride and recovering amorphous form of fexofenadine hydrochloride from the solution thereof by spray drying or freeze drying technique.

In yet another aspect of this invention, there is provided a pharmaceutical composition comprising fexofenadine hydrochloride in an amorphous form with one or more pharmaceutical carriers and/or excipients.

DETAILED DESCRIPTION OF THE INVENTION

In a preferred embodiment of the invention, fexofenadine hydrochloride is recovered from the solution in an amorphous form using a freeze drying

technique. The freeze dryer (Model : Virtis Genesis SQ Freeze – Dryer), which is used, operates on the principle of lyophilization, i.e., a process of stabilizing initially wet materials (aqueous solution or suspensions) by freezing them, then subliming the ice while simultaneously desorbing some of the bound moisture (primary drying). Following disappearance of the ice, desorption may be prolonged (secondary drying). This process is preferably conducted under vacuum.

In a more preferred embodiment of the invention, fexofenadine hydrochloride is recovered from the solution in an amorphous form using a spray drying technique. The Mini-Spray Dryer (Model : Buchi 190, Switzerland) which is used, operates on the principle of nozzle spraying in a parallel – flow, i.e., the sprayed product and the drying gas flow in the same direction. The drying gas can be air or inert gases such as nitrogen, argon and carbon dioxide. Nitrogen is preferred in this case.

The term "suitable solvent" means lower alkanol or combination of lower alkanol, ester, ketone, chlorinated solvent and mixture (s) thereof. Lower alkanol includes those primary, secondary and tertiary alcohols having from one to six carbon atoms. Suitable lower alkanol solvents include methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, amyl alcohol and t-butanol. The term ketone or ester includes solvents having from one to ten carbon atoms such as acetone, methyl ethyl ketone, 2-butanone, 4-methylpentan-2-one, ethyl acetate or n-butylacetate. The suitable chlorinated

solvents include dichloromethane, chloroform or carbon tetrachloride. Mixture of these solvents are also contemplated.

Amorphous fexofenadine hydrochloride prepared according to the process of the present invention may be characterized by its infra-red spectrum in KBr disc (Figure 1) and by its X-ray powder diffraction pattern (Figure 2). The infra red spectrum in KBr (Figure 1) obtained for the samples prepared by the process of the present invention is different than infra red spectrum in KBr for crystalline form (Figure 3) of fexofenadine hydrochloride obtained per WO patent application (WO 95/31437). X-ray powder diffraction patterns gave a plain halo (Figure 2) and show no peaks which are characteristic of a crystalline fexofenadine hydrochloride (Figure 4) thus demonstrating the amorphous nature of the product.

The present invention is illustrated by the following examples which are not intended to limit the effective scope of the claims.

Preparation of amorphous fexofenadine hydrochloride by Spray Drying using crystalline fexofenadine hydrochloride

EXAMPLE 1

Fexofenadine hydrochloride crystalline (124g, 0.231 moles) was dissolved in methanol (300ml) at 25-30ºC. The clear solution so obtained was subjected to spray drying in a Mini-Spray Dryer (Buchi Model 190) and fexofenadine hydrochloride in an amorphous form was isolated (114g).

X-ray powder diffraction pattern (Figure 2) shows a plain halo thus demonstrating the amorphous nature of the product. Infrared spectrum in KBr (Figure 1) is different than the one obtained for crystalline form of fexofenadine hydrochloride (Figure 3).

EXAMPLE 2

The process of Example 1 was repeated with fexofenadine hydrochloride (10g, 0.0186moles) using ethylacetate (20ml) and methanol (20ml) instead of methanol to give amorphous fexofenadine hydrochloride (9.2g). IR (KBr) spectrum and x-ray crystallography confirmed that the material was amorphous in nature.

EXAMPLE 3

The process of Example 1 was repeated with fexofenadine hydrochloride (10g, 0.0186 moles) using acetone (20ml) and methanol (20ml) instead of methanol to give amorphous fexofenadine hydrochloride (8.9g). IR (KBr) spectrum and x-ray crystallography examination confirmed the amorphous nature of the product.

Preparation of amorphous fexofenadine hydrochloride by spray drying using fexofenadine base.

EXAMPLE 4

Fexofenadine (15gm, 0.0299 moles) was suspended in methanol (60 ml) and to it was added isopropanol containing equivalent molar hydrogen

chloride to get a clear solution. The clear solution was subjected to spray drying in a mini spray dryer (Buchi Model 190) and fexofenadine hydrochloride in an amorphous form was isolated (14.9g). IR (KBr) and x-ray crystallography revealed that the product was amorphous.

EXAMPLE 5

The process of Example 4 was repeated with fexofenadine (10g, 0.0199 moles) using methanol (40ml) and to it was added methanol containing equimolar hydrogen chloride to give amorphous fexofenadine hydrochloride (9.5g). IR (KBr) spectrum and x-ray crystallography examination confirmed the amorphous nature of the product.

WE CLAIM :

1. Fexofenadine hydrochloride in an amorphous form.

2. A pharmaceutical composition containing a therapeutically effective amount of the amorphous form of claim 1 together with one or more pharmaceutical carriers or excipients.

3. A process for the preparation of fexofenadine hydrochloride in an amorphous form which comprises dissolving crystalline fexofenadine hydrochloride in a suitable solvent or dissolving fexofenadine base in a suitable solvent and adding a suitable solvent containing hydrogen chloride and recovering fexofenadine hydrochloride from said solution by spray drying or freeze drying technique.

4. The process of claim 3, wherein suitable solvent is selected from the group consisting of lower alkanol, ester, ketone, chlorinated solvent and mixtures thereof.

5. The process of claim 4, wherein lower alkanol includes primary, secondary and tertiary alcohols having from one to six carbon atoms.

6. The process of claim 5, wherein said lower alkanol is selected from the group consisting of methanol, ethanol, n-propanol, isopropanol or n-butanol and mixtures thereof.

7. The process of claim 6, wherein the solvent is methanol, ethanol or isopropanol.

8. The process of claim 4, wherein the ester solvent is selected from ethyl acetate or n-butyl acetate.

9. The process of claim 4, wherein the ketone solvent is acetone, methylethyl ketone, 2-butanone, 4-methylpentan-2-one.

10. The process of claim 4, wherein the chlorinated solvent is chloroform, dichloromethane or carbontetrachloride.

11. The process of claim 3, wherein fexofenadine hydrochloride in an amorphous form is isolated from said solution by spray drying.

12. The process of claim 3, wherein the spray drying is effected in the presence of an inert gas.

13. The process of claim 3, wherein fexofenadine hydrochloride in an amorphous form is isolated from said solution by freeze drying.

FIG. 1

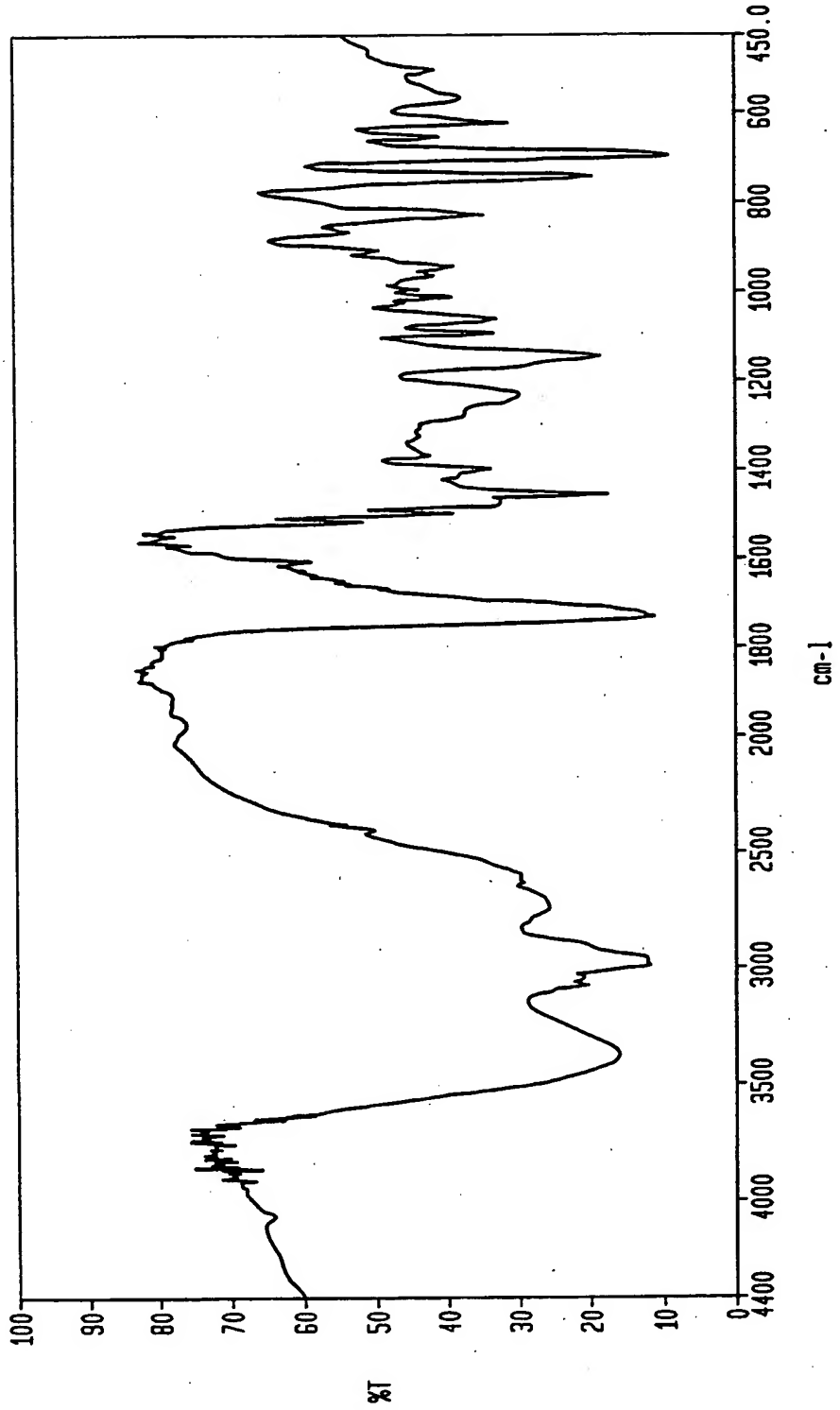

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FIG. 2

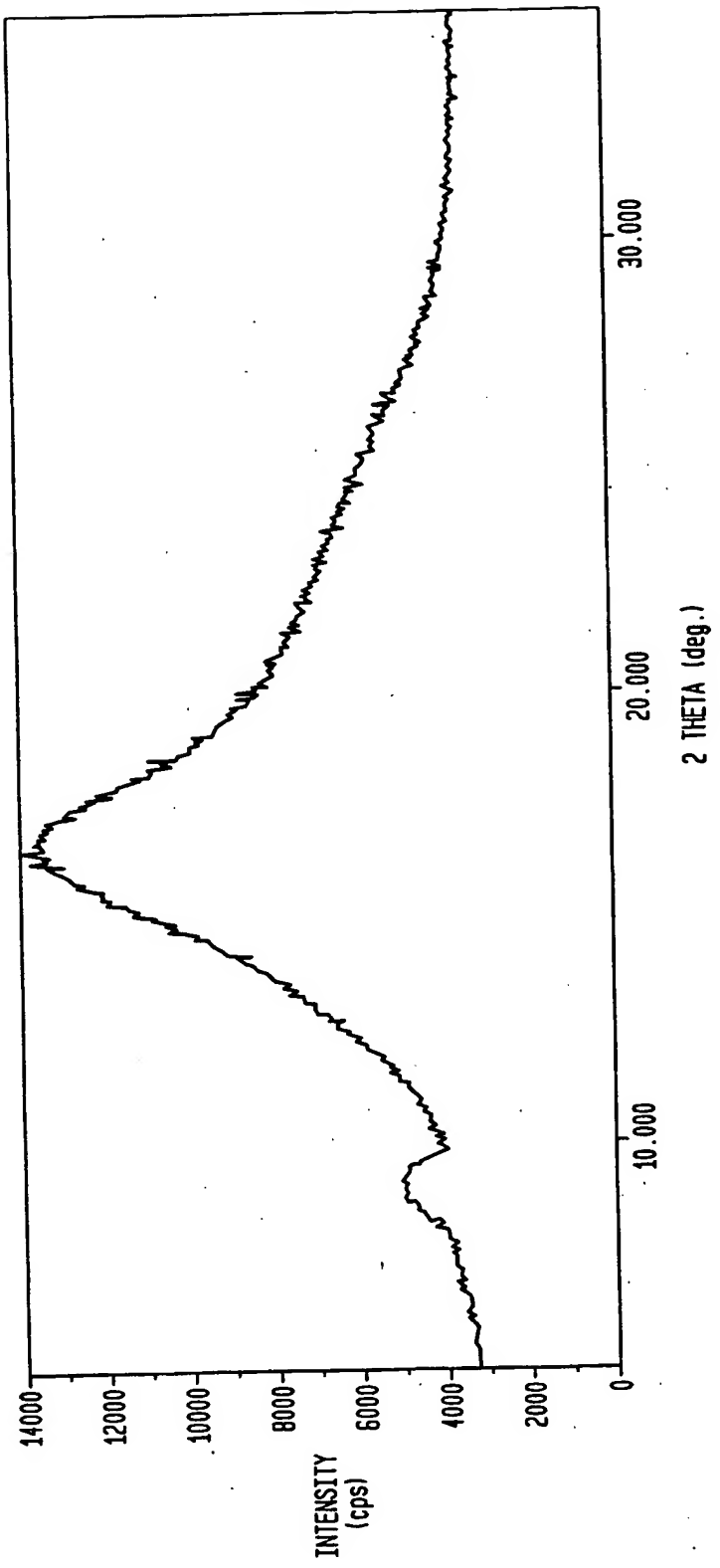
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FIG. 3

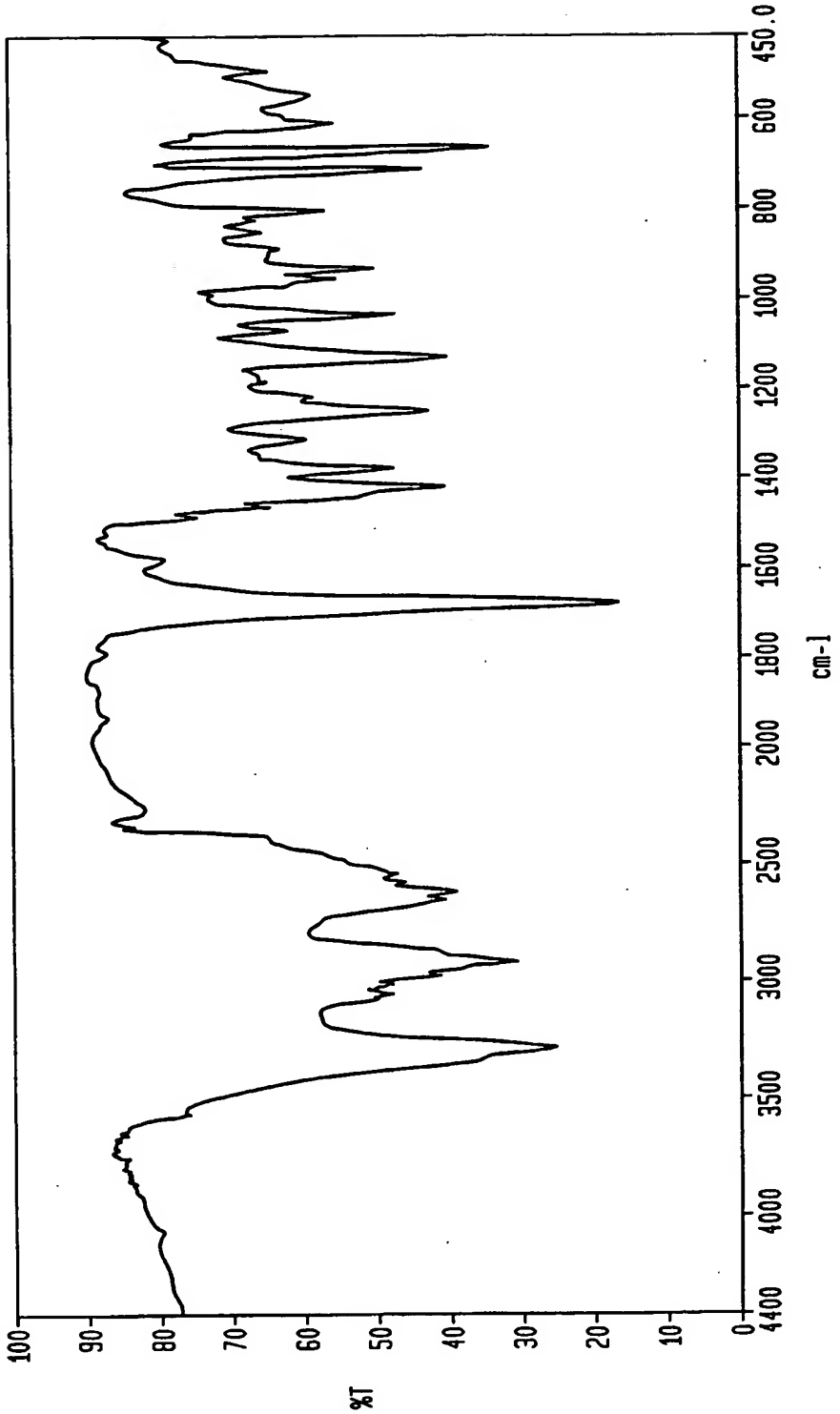
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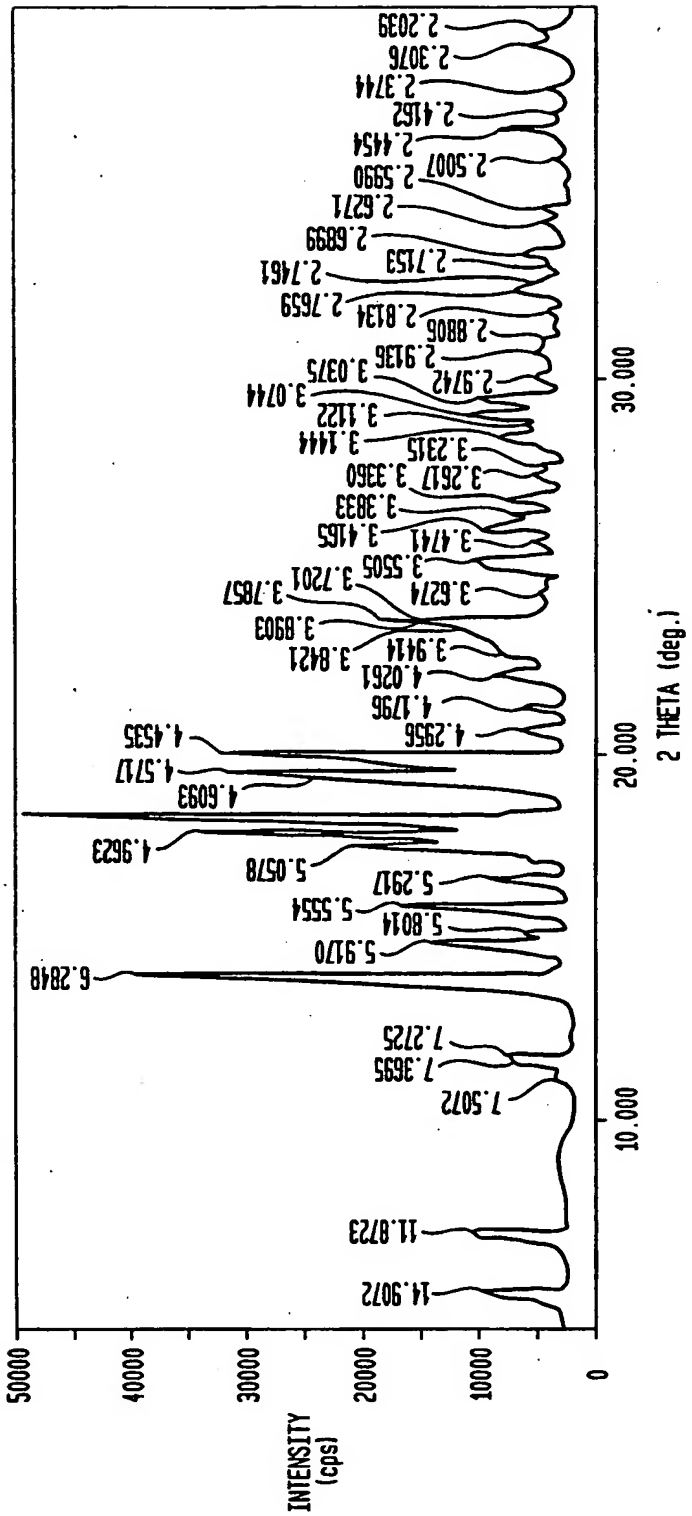
FIG. 4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20.000
30.000
2 THETA (deg.)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB00/00708

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) :A61K 31/445; C07D 211/22, 34
US CL :514/317; 546/239, 240

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

U.S. : 514/317; 546/239, 240

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

CAS--structure
EAST/WEST-- subclasses and image

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	US 4,254,129 A (CARR ET AL.) 03 March 1981, see entire document, especially column 13, example 3.	1-2
Y	US 4,285,957 A (CARR ET AL.) 25 August 1981, see entire document, especially column 13, example 3.	1-2
Y	WO 95/31437 A1 (MARION MERREL DOW INC.) 23 November 1995, see entire document, especially claims 10-11, 13-15, 17-19.	1-13
Y	LIEBERMAN, Herbert A. Pharmaceutical dosage forms. New York, Marcel Dekker, Inc., 1989, Volumn 2 page 463, see entire document.	1-13

[X] Further documents are listed in the continuation of Box C. [ ] See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
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Date of the actual completion of the international search 05 SEPTEMBER 2000	Date of mailing of the international search report 11 OCT 2000
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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IB00/00708

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
Y	SUZUKI, E. et al. Studies on method of particle size ruduction of medicinal compounds. VIII.[1)] Size reduction by freeze-drying and the influence of pharmaceutical adjuvants on the micromeritic properties of freeze-dried powders. Chem. Pharm. Bull. 1979, Vol. 27, No. 5, pages 1214-1222, see entire article.	1-13
Y	Database CAS on STN (COLUMBUS, OH, USA) Accession No. 98:166814, CORRIGAN et al. Physicochemical properties of spray dried drugs: phenobarbitone and hydroflumethiazide. Abstract, Drug Dev. Ind. Pharm. 1983, Vol. 9, No. 1-2, pages 1-20, see entire article.	1-13
Y	Database CAS on STN (COLUMBUS, OH, USA) Accession No. 86:8603, NUERNBERG, E. Colloidal distribution states in pharmaceutical technology. Manufacture and qualities of pharmaceutical preparations by spray drying. Abstract, Prog. Colloid Polym. Sci. 1976, Vol. 59, pages 55-59, see entire article.	1-13